REVIEW ARTICLES

MEDICAL PROGRESS

PRIMARY PREVENTION OF STROKE

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STROKE is the third leading cause of death in the United States, after coronary heart disease and cancer. There are approximately 500,000 cases of stroke each year; of these, 150,000 are fatal.[1] Many survivors are left with mental and physical impairment and require assistance with activities of daily living. Twenty-eight percent of patients with stroke are under 65 years of age, and women account for 40 percent of the new cases.[2] Blacks in the United States have a rate of mortality due to stroke roughly twice that of whites.[3] There are over 3 million patients with stroke alive in the United States today,[4] and the cost of acute and long-term care for such patients is approximately $30 billion per year.[5] There are currently no effective treatments for most forms of stroke. Hence, primary prevention offers the greatest potential for reducing the burden of this disease.

A gradual decline in mortality due to stroke in the United States began in the 1920s and accelerated in the 1970s to about 5 percent per year[6] (Fig. 1). Data from Rochester, Minnesota, indicate a decline in the incidence of most forms of stroke, beginning in the 1950s for women and the 1960s for men.[8] The incidence of ischemic stroke declined the most, but rates of intracerebral hemorrhage fell as well. The incidence of subarachnoid hemorrhage has remained unchanged during this period. In recent years, however, the decline in mortality due to stroke has continued, but at a slower rate of 2 to 3 percent per year.[9] This recent slowdown may be due to the increased detection of less severe cases of stroke by computed tomography.[10]

Mortality due to stroke varies widely among countries, but within most countries, the rates in men and women are similar. From 1989 through 1992, mortality due to stroke was 253 per 100,000 men and 208 per 100,000 women in Portugal; in the United States, the rates — among the lowest worldwide — were 59 and 57 per 100,000 men and women, respectively (Fig. 2). In most countries, as in the United States, mortality due to stroke has been declining. Most of this decline is probably attributable to changes in lifestyle, as can be seen in data on men born in Japan who now reside in Japan, Hawaii, and California.[12] Their rates of mortality due to stroke were similar to those of the native-born population around them, which suggests that environmental factors strongly influence the risk of stroke (Fig. 3).

Stroke is a heterogeneous disorder that encompasses cerebral infarction (ischemic stroke), intracerebral hemorrhage, and subarachnoid hemorrhage. Cerebral infarction is the most common form of stroke, and findings from studies of broadly defined stroke are most applicable to ischemic stroke. Moreover, within the major categories of stroke are many subtypes. Research on stroke has been limited by the inadequate classification of subtypes and by variations in coding and surveillance.[13] These difficulties have hampered the interpretation of epidemiologic studies. In this article, we review clinical and epidemiologic data related to the primary prevention of stroke and attempt to provide "best estimates" of the reductions in risk that can be expected among patients who successfully modify their risk factors (Table 1).[14] We use the terms "ischemic stroke" and "hemorrhagic stroke" to denote the two broad categories of stroke, with thrombotic and embolic subtypes included in the first category and subarachnoid and intracerebral hemorrhage included in the second.

HYPERTENSION

Hypertension is currently the most consistently powerful predictor of stroke; it is a factor in nearly 70 percent of strokes.[15] Hypertension promotes stroke by aggravating atherosclerosis in the aortic arch and cervicocerebral arteries; causing arteriosclerosis and lipohyalinosis in the small-diameter, penetrating end arteries of the cerebrum; and contributing to heart disease, of which stroke is a complication.[16] For people of all ages and both sexes, higher levels of both systolic and diastolic blood pressure have been associated with an increased incidence of ischemic and hemorrhagic stroke.[17-19] A recent meta-analysis reported a 10-to-12-fold increase in the risk of stroke for people in the highest category of diastolic blood pressure (mean, 105 mm Hg), as compared with the lowest (mean, 76 mm Hg).[20]

Although the value of treating severe hypertension has been known for some time,[21] only recently has the treatment of mild-to-moderate hypertension been extensively studied. A recent meta-analysis of the association between treatment to lower blood pressure and cardiovascular disease surveyed 14 clinical trials to assess the effect of drug therapy — primarily with diuretics or beta-blockers — on the incidence of stroke and

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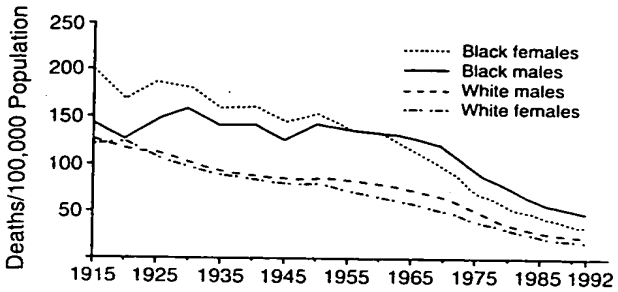

Figure 1. Trends in Age-Adjusted Mortality from Stroke in the United States According to Sex and Race, 1915 through 1992. Data are from the National Heart, Lung, and Blood Institute.[7]

fatal stroke.[22] In all the studies combined, there was a 42 percent reduction (95 percent confidence interval, 33 to 50 percent) in the incidence of stroke and a 45 percent reduction (95 percent confidence interval, 30 to 58 percent) in the incidence of fatal stroke associated with a decrease in diastolic blood pressure of 5 to 6 mm Hg. These reductions in risk were apparent at all levels of blood pressure. In elderly patients (more than 60 years of age), antihypertensive therapy has decreased the risk of stroke by a range of 25 percent (95 percent confidence interval, 3 to 42 percent)[23] to 47 percent (95 percent confidence interval, 14 to 67 percent).[24] These studies did not compare the effects of drug treatment on ischemic stroke with the effects on hemorrhagic stroke.

Isolated systolic hypertension (systolic pressure, >160 mm Hg, and diastolic pressure, <90 mm Hg), which is uncommon before the age of 45, increases steadily after the age of 55. It is more common in women than in men, and it affects about 30 percent of people 65 to 74 years of age.[25] In the Systolic Hypertension in the Elderly Program, reductions of 11 mm Hg in mean systolic pressure and 3.4 mm Hg in mean diastolic pressure in the treatment group led to a decline in the risk of stroke of 36 percent (95 percent confidence interval, 18 to 50 percent).[26] This association was observed in patients of all ages and both sexes. These findings are supported by the Medical Research Council study,[23] and another trial is under way.[27]

There is very strong and consistent evidence in support of the use of antihypertensive therapy to reduce the risk of stroke in all classes of patients with hypertension. The Joint National Committee on High Blood Pressure, among others, has suggested that nonpharmacologic treatment should be prescribed first for mild-to-moderate hypertension[28,29] (Table 2). Although these strategies for the reduction of blood pressure have implications for the primary prevention of stroke, this issue needs to be studied directly.

Smoking

Cigarette smoking is a major cause of both ischemic and hemorrhagic stroke. Smoking may contribute to stroke by increasing blood levels of fibrinogen and other clotting factors[31]; increasing platelet aggregability[32]; decreasing high-density lipoprotein cholesterol levels[33]; increasing the hematocrit[34]; directly damaging endothelium, which may lead to atherosclerosis[35]; and acutely increasing blood pressure, which may promote arterial rupture.[36] In a recent meta-analysis of observational data,[37] the summary estimate of the relative risk of stroke for smokers, as compared with nonsmokers, was 1.51 (95 percent confidence interval, 1.45 to 1.58). The risk of stroke for smokers was higher for women than for men; it decreased with increasing age and increased with the number of cigarettes smoked per day. The population attributable risk (the proportion of the instances of stroke that would be avoided if the risk factor were not present) due to smoking, for stroke of all types, is 12 percent.

The risk of stroke for former smokers has consistently been found to be lower than that for current smokers. In the meta-analysis just cited, the pooled relative risk of all types of stroke for former smokers, as compared with persons who had never smoked, was 1.17 (95 percent confidence interval, 1.05 to 1.30); for persons under 75 years of age, the relative risk was 1.47 (95 percent confidence interval, 1.15 to 1.88). In two recent studies, both male and female former smokers decreased

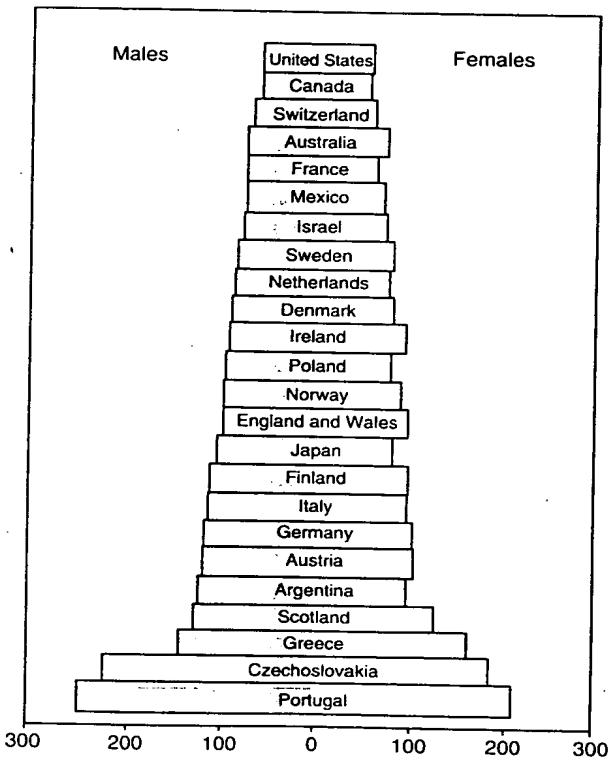

Figure 2. Average Annual Age-Adjusted Mortality from Cerebrovascular Disease According to Sex, 1989 through 1992. Data are from the World Health Organization.[11] Rates have been adjusted to the age distribution of the U.S. population.

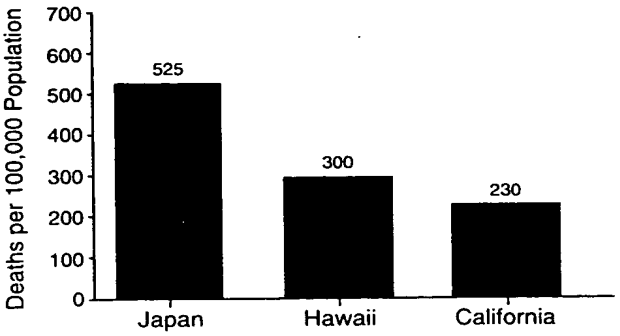

Figure 3. Mortality from Stroke among Japanese-Born Men 55 to 64 Years of Age Residing in California, Hawaii, and Japan, 1950.
Modified from Reed,[12] with the permission of the publisher.

their risk of stroke of all types to the level of nonsmokers two to five years after quitting.[38,39] Clinical trials to assess the effect of the cessation of smoking on the risk of stroke have been hampered by methodologic problems.[40] Although there is no conclusive evidence from such trials, observational studies comparing former and current smokers suggest that quitting is highly beneficial.

Glucose Tolerance

Epidemiologic and clinical data support the association of diabetes with a higher-than-normal prevalence of risk factors for cardiovascular disease, such as hypertension, obesity, and dyslipoproteinemia.[41] Although the association between diabetes and stroke may operate through such risk factors, many studies have observed an independent association — in both men and women — of diabetes with an elevated risk of stroke,[17,42,43] with relative risks of ischemic stroke and stroke of all types of 1.8 to 3.0 for both diabetic men and diabetic women. As for hemorrhagic stroke,[42,43] only one study has found an association with diabetes; this was a nonsignificant elevation in the risk of subarachnoid hemorrhage for patients with diabetes (relative risk, 2.0; 95 percent confidence interval, 0.7 to 6.4).[43] The population attributable risk due to diabetes is between 2 and 5 percent for stroke of all types. There is also evidence to support a positive association between the degree of glucose intolerance and an increased risk of stroke.[42] Postulated mechanisms for the independent positive association between diabetes and the risk of stroke include glycosylation of tissue proteins, leading to accelerated atherogenesis[44] and enhanced thrombosis due to decreased fibrinolytic activity, increased platelet aggregation and adhesiveness, and elevated levels of fibrinogen, factor VII, and factor VIII.[45]

Non-insulin-dependent diabetes mellitus (NIDDM) affects at least 90 percent of the 14 million people with diabetes in the United States. The major modifiable risk factors for NIDDM are adiposity (both total fat and centrally distributed body fat)[29] and physical inactivity.[46] The influence of strict glycemic control on the risk of stroke remains uncertain. The treatment of the traditional risk factors for cardiovascular disease associated with diabetes may be at least as beneficial in the prevention of macrovascular disease in diabetic patients as are efforts to lower blood glucose alone,[41] but evidence is lacking about the magnitude of the effect.

Obesity

Epidemiologic and clinical data support the association of obesity with hypertension, dyslipidemia, hyperinsulinemia, and glucose intolerance.[29] In part because of the association of obesity with these risk factors for cardiovascular disease, many studies have found a pos-

Table 1. Available Data on the Primary Prevention of Stroke.

Intervention	Source of Data	Findings*
Treatment of hypertension	Meta-analysis of randomized trials	42% reduction in the risk of stroke with a decrease of 5 to 6 mm Hg in diastolic blood pressure 36% reduction with decreases of 11 mm Hg in systolic pressure and 3.4 mm Hg in diastolic pressure in patients with isolated systolic hypertension
Cessation of smoking	Meta-analysis of observational studies, two large prospective cohort studies	30 to 40% reduction among former smokers as compared with current smokers 2 to 5 years after cessation of smoking
Normalization of glucose tolerance	Observational studies	Data currently insufficient to provide estimates
Avoidance of obesity	Observational studies	Data currently insufficient to provide estimates
Promotion of physically active lifestyle	Observational studies	30% reduction associated with maintenance of an active as compared with a sedentary lifestyle
Treatment of high cholesterol levels	Meta-analysis of randomized trials	No association observed between cholesterol-lowering regimens and the risk of stroke
Dietary modification	Observational studies, limited randomized trials	Data currently insufficient to provide estimates of risk related to intake of dietary fats, fatty acids, and antioxidant vitamins Decreased risk of ischemic stroke and increased risk of hemorrhagic stroke in those who consume a moderate amount of alcohol
Prophylactic low-dose aspirin	Observational studies, randomized trials	Data currently insufficient to provide estimates
Low-dose oral contraceptives	Meta-analysis of observational studies	Data currently insufficient to provide estimates
Postmenopausal estrogen-replacement therapy	Meta-analysis of observational studies	No apparent association with risk of stroke

*Estimated reductions in risk refer to the independent contribution of each risk factor and do not address any interactions among them.

Table 2. Risk-Reduction Objectives from Healthy People 2000 and Strategies for Achieving Them.*

Risk Factor	Prevalence before 1990	Current Prevalence	Objective	Strategies
	percent			
Hypertension (blood pressure, ≥140/90 mm Hg)	30†	26	No objective set‡	Weight reduction, promotion of physical activity, biofeedback, stress reduction, reduced alcohol intake, reduced salt intake, increased potassium intake
Smoking	29§	27¶	15	Counseling by physician, nicotine skin patch, nicotine polacrilex gum, hypnosis, acupuncture, aversive conditioning, behavioral modification
High serum cholesterol (≥240 mg/dl [6.20 mmol/liter])	27‖	20¶	20	Dietary modification, drug therapy
Obesity (≥20% above desirable weight)	26‖	34**	20	Hypocaloric diet, promotion of physical activity, nutrition education, behavioral modification, psychological and social support
Physical inactivity	24†	24††	15	Counseling by physician, work-site fitness programs, community fitness facilities
Diabetes	2.8§	2.8¶	2.5	Weight reduction, promotion of physical activity

*Prevalence figures and objectives are from the Public Health Service.[30]
†1985.
‡No objective has been set for the population as a whole, but among people with known hypertension, the goal is to reduce blood pressure in 50 percent of them to under 140/90 mm Hg.
§1987.
¶1992.
‖1976–1980.
**1988–1991.
††1991.

itive association between obesity and the risk of fatal and nonfatal stroke (the relative risks generally range from 1.5 to 2.0).[17,47-52] These studies did not assess the effect of obesity on the risk of ischemic as opposed to hemorrhagic stroke. For stroke of all types, the population attributable risk due to obesity is between 15 and 25 percent. An independent association has also been observed between obesity and stroke.[17,51-53] In addition, higher weight during young adulthood and weight gain after young adulthood may also be risk factors for stroke.[47,48]

Recent studies have also assessed measurements of the distribution of body fat as predictors of stroke, specifically the waist-to-hip ratio,[54,55] subscapular skin-fold thickness,[56,57] and waist circumference.[57] Direct associations have been found in these studies, and in some cases, the association was independent of other traditional risk factors for cardiovascular disease.[54,56] Some mechanisms have been proposed for the association between abdominal obesity and cardiovascular risk factors. Increased peripheral concentrations of insulin[58] and increased triglyceride concentrations,[59] associated with abdominal obesity, may be due to the direct deposition of free fatty acids into the portal vein from intra-abdominal adipocytes. Also, elevated blood pressure may be associated with abdominal obesity.[60]

At present, about one in three adults in the United States is classified as overweight, and the prevalence of obesity has been steadily increasing.[61] Because obesity may increase the risk of stroke by its adverse effects on other risk factors for cardiovascular disease, efforts to reduce weight should be beneficial.[62]

Physically Active Lifestyle

Although the relation between physical activity and the risk of stroke has not been extensively examined, the results from available studies are quite consistent. Several studies have found a statistically significant inverse relation between physical activity and the risk of stroke in men[63-65] and women.[66] This inverse relation was also observed with ischemic and hemorrhagic stroke considered separately.[63] Physical activity favorably affects risk factors for cardiovascular disease.[67-69] Exercise tends to decrease the aggregability of platelets,[67] increase sensitivity to insulin,[68] reduce weight, increase high-density lipoprotein cholesterol levels, and lower blood pressure.[69]

Despite the apparent benefits of physical activity with respect to cardiovascular disease,[70] mortality from all causes,[71] and psychological health,[72] a sedentary lifestyle has predominated in the United States during the past several decades. Among people 18 to 74 years of age, only 24 percent reported moderate physical activity and only 14 percent reported vigorous activity.[30] Therefore, efforts are needed to increase levels of physical activity, especially in patients with underlying cardiovascular risk factors.

Serum Cholesterol

The relation between serum cholesterol levels and the risk of stroke is not clear. A U-shaped relation between the serum level of total cholesterol and the risk of stroke of all types has been proposed, derived from an inverse association with hemorrhagic stroke and a direct association with ischemic stroke. The inverse relation with hemorrhagic stroke has been observed in numerous studies of populations of Japanese origin[73-75] and among white men studied in the Multiple Risk Factor Intervention Trial.[76] The postulated direct association with ischemic stroke, however, has not been consistently observed.[17,75,77] Data on women are very scant and reveal no clear patterns.[17,78] Data concerning lipid subtypes are also few and inconsistent.[79-81]

Possible differences in the effects of cholesterol at different vascular sites could lead to the complex association between serum cholesterol levels and stroke.[82] An increase in serum cholesterol could lead to atherosclerosis of the internal carotid artery and the larger cerebral arteries and to subsequent ischemic stroke. A

second mechanism, more speculative, involves the weakening of the endothelium of smaller intracerebral arteries due to low serum cholesterol levels. This condition may be further aggravated by hypertension and lead to hemorrhagic stroke.[75,76]

In a recent meta-analysis,[83] an increase in the risk of fatal stroke (odds ratio, 1.32; 95 percent confidence interval, 0.94 to 1.86) and a decrease in the risk of nonfatal stroke (odds ratio, 0.88; 95 percent confidence interval, 0.70 to 1.11) was observed among men in all trials of intervention to lower lipid levels through drugs or diet. When treatment with clofibrate was examined alone, it was associated with an increase in the risk of fatal stroke (odds ratio, 2.64; 95 percent confidence interval, 1.42 to 4.92) and a decrease in the risk of nonfatal stroke (odds ratio, 0.87; 95 percent confidence interval, 0.61 to 1.26). There was no appreciable association between treatments other than clofibrate and either fatal stroke (odds ratio, 1.04; 95 percent confidence interval, 0.70 to 1.55) or nonfatal stroke (odds ratio, 0.93; 95 percent confidence interval, 0.71 to 1.23). In the studies in which ischemic stroke was assessed independently, a statistically significant decrease in risk was observed.

Despite these only preliminary results, the consistently deleterious role of high serum cholesterol levels in the development of coronary heart disease mandates continued support of programs to lower serum cholesterol levels by lowering the intake of cholesterol and saturated fat. There is, however, a need to explore more carefully the effects of low serum cholesterol levels — especially those below 160 mg per deciliter (4.13 mmol per liter)[76] — on the subtypes of hemorrhagic stroke, as well as the possible augmentation of these effects by hypertension.

Diet

Alcohol

The relation of moderate alcohol consumption to the risk of stroke has not been conclusively determined. Several methodologic problems have hampered research, including the contamination of the reference group of lifelong abstainers with former drinkers, which may contribute to the J-shaped relation observed in many studies (i.e., ostensible nondrinkers appear to have a higher risk than moderate drinkers). On the basis of observational data, mainly from cohort studies, two models have been proposed to describe the relation between moderate alcohol consumption and the risk of stroke.[84] There appears to be a dose–response relation between moderate alcohol consumption and the risk of intracerebral and subarachnoid hemorrhage, with increased risk apparent even at low levels of intake.

With respect to ischemic stroke, though, findings in white and Japanese populations seem to differ. In studies of predominantly white groups, an inverse association with ischemic stroke is seen at low levels of alcohol intake; among the Japanese, no association is present at low levels of intake, whereas the risk increases at a higher level of consumption. Overall, the relative risk of ischemic stroke associated with moderate alcohol consumption (one to two drinks a day), as compared with nondrinking, is between 0.3 and 0.5 in some populations; it increases to 2 for persons consuming three or more drinks per day. For hemorrhagic stroke, the relative risk varies from 2 to 4, with some increased risk at all levels of intake.

The mechanisms by which moderate alcohol intake may, in fact, be beneficial include a reduction in the risk of coronary heart disease,[85] favorable modification of blood lipid and lipoprotein levels,[86] and inhibition of clotting mediated by increases in prostacyclin levels and activation of the fibrinolytic system.[87] Higher levels of alcohol intake, however, may induce cardiac arrhythmia,[88] increase blood pressure[89] and cerebral blood flow,[90] and adversely affect the coagulation system.[91]

Alcoholism is a major public health problem in this country. Over 10 million adults have alcoholism and alcohol-related diseases such as hypertension and cirrhosis.[92] Alcohol has also been implicated in 50 percent of all accidental deaths, suicides, and homicides.[93] Despite the potential benefit of moderate alcohol consumption, alcohol should not be considered as a preventive agent for stroke, given the health risks associated with excessive intake.

Fat and Fatty Acids

There are few data on the association between the intake of fatty acids (saturated, monounsaturated, and polyunsaturated fats, excluding fish oils) and stroke. Associations between dietary consumption of these lipids and serum cholesterol and lipoprotein levels have been documented, however.[94] Given the uncertain association between serum lipid levels and the risk of stroke, it is not surprising that the specific nature of the relation between dietary fat and stroke requires elucidation.

Population studies suggest that the combined intake of saturated, monounsaturated, and polyunsaturated fats is inversely correlated with fatal stroke.[73] No appreciable associations have been noted in most observational studies that assessed saturated-fat intake and the risk of stroke.[95,96]

With respect to the consumption of polyunsaturated fatty acids derived from fish oils (n−3 fatty acids), no association was observed between fish intake and stroke in one study,[97] although another recent cohort study reported an inverse relation between fish consumption and the risk of stroke (relative risk, 0.49; 95 percent confidence interval, 0.24 to 0.99).[98] Data from Japan also support an inverse relation between fish intake and the risk of stroke of all types.[99] The consumption of fish may inhibit stroke through decreased platelet aggregation and blood viscosity, increased fibrinolytic activity, and decreased blood pressure.[100]

No clear conclusions can be derived from these data on dietary fat intake and stroke. Because of the postulated difference in the effects of serum lipids on ischemic and hemorrhagic stroke, the relation between fat intake and all types of stroke combined is not likely to

be linear. It is therefore necessary to evaluate separately the fractions of dietary fat and their relation to the subtypes of stroke in order to understand fully whatever connections may exist between them.

Antioxidants

Evidence is mounting to suggest a role for antioxidant vitamins (beta carotene and vitamins E and C) in the prevention of cardiovascular disease. Antioxidants are thought to protect cellular components from the highly reactive species of free radicals that may develop either in normal endogenous oxidative metabolism or from external sources. Free radical species have been shown to damage low-density lipoprotein cholesterol through oxidation, which in turn may increase atherogenesis.[101] In addition, free radicals may directly alter endothelial function,[102] promote thrombosis,[103] and interfere with normal vasomotor regulation.[104] Randomized trials have shown either an inverse association[105,106] or no association[107] between consumption of antioxidant vitamins and the risk of stroke. Similarly, some observational studies indicate an inverse relation between the intake of antioxidant vitamins and the risk of stroke,[108,109] although others find no association.[96,110] The increased consumption of fruits and vegetables has also been linked to a reduced risk of stroke.[111]

The relative values of food and supplementation as sources of these micronutrients need elucidation. Although public health recommendations to increase fruit and vegetable consumption to at least five servings per day are warranted and may lead to reductions in the risk of stroke, it remains premature to recommend vitamin supplementation for this purpose. Several ongoing randomized clinical trials of antioxidant supplements in the prevention of cardiovascular disease will soon provide evidence on this issue.[112,113]

Low-Dose Aspirin

The role of antiplatelet therapy in the primary prevention of cardiovascular disease has gained considerable attention over the past two decades because of the established benefits of aspirin in the secondary prevention of major vascular events. The medical and surgical treatment of populations at high risk for cardiovascular disease and stroke has been reviewed in detail elsewhere.[114,115]

However, despite conclusive evidence of the benefits of aspirin in the secondary prevention of stroke, only two clinical trials have been conducted that address primary prevention. In the United States, the Physicians' Health Study found an increased risk of hemorrhagic stroke (relative risk, 2.14; 95 percent confidence interval, 0.96 to 4.77) among men given 350 mg of aspirin every other day for an average of 60.2 months.[112] The relative risks of ischemic stroke and stroke of all types were 1.11 (95 percent confidence interval, 0.82 to 1.50) and 1.22 (95 percent confidence interval, 0.93 to 1.60), respectively. The British Doctors' Trial gave participants a daily dose of 500 mg of aspirin for six years and found no significant difference in the incidence of stroke between the treatment and control groups, but it did find a higher incidence of disabling stroke among those taking aspirin (relative risk, 2.58; $P<0.05$).[116] Data are also available from two large cohort studies. No association between aspirin use and ischemic or hemorrhagic stroke was found in a study of women,[117] but a nonsignificant increase in the risk of stroke of all types was observed in a group of elderly patients.[118]

It remains unclear whether aspirin is beneficial in the primary prevention of ischemic stroke and whether it increases the risk of hemorrhagic stroke. Despite the existence of data from large-scale randomized trials and prospective cohort studies, there were not enough stroke end points in those studies to allow definite conclusions to be drawn. The issue of dosage should also be kept in mind, because dose-related gastrointestinal (and other) side effects of aspirin have been documented,[119] aside from the possible increased risk of hemorrhagic stroke. Furthermore, the effects, and the risk–benefit ratio, of treatment with aspirin may be different in women and men.[120] A randomized trial of aspirin in the primary prevention of cardiovascular disease in women, which is testing low doses of aspirin (100 mg every other day), is in progress and will provide results within several years.[113]

Women and Hormone Treatment

Low-Dose Oral Contraceptives

Since the introduction of oral contraceptives in the early 1960s, both beneficial and detrimental effects have been documented.[121] Higher-dose formulations of oral contraceptives were found to increase the risk of stroke in some subgroups of women, including women over 35 years of age, cigarette smokers, women with hypertension, and women with a history of migraine headaches.[122-124] The amounts of estrogen and progestogen in oral contraceptives have been reduced considerably since the introduction of the drugs because of concern about adverse effects, such as increased thrombosis and high blood pressure.[125,126]

A recent meta-analysis combined the results of 47 case–control and cohort studies and established a relative risk among users of 1.8 (95 percent confidence interval, 1.6 to 2.0) for stroke of all types combined.[127] The data in that analysis are from studies that used both high- and low-dose hormone formulations. No association between oral-contraceptive use and stroke was observed in some recent cohort studies,[128-131] including two studies that assessed low-dose regimens.[130,131] However, an increased risk of subarachnoid hemorrhage[131] and an increased risk of stroke[132] have been observed.

Current information is insufficient to permit a definitive statement about the risk of stroke in women who use the new-formulation oral contraceptives. There is a suggestion, however, that fewer adverse outcomes were observed in women who took low-dose oral contraceptives than in those who took a high-dose form. Further research is needed, but in the interim, care should be

exercised in prescribing oral contraceptives to women at high risk for stroke.

Postmenopausal Estrogen-Replacement Therapy

Postmenopausal therapy with exogenous estrogen is widely used to relieve the symptoms of menopause and prevent osteoporosis. Moreover, the use of exogenous estrogen has been associated with a 44 percent reduction in the risk of coronary heart disease in observational studies.[70] Postulated mechanisms for this protection include a favorable effect on serum lipid levels, reducing total and low-density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol[133]; the inhibition of endothelial hyperplasia[134]; and the enhanced production of prostacyclin.[135] Despite the expected benefits of therapy, though, there is some concern about the risk of stroke.

A recent meta-analysis of relevant studies has estimated the relative risk of stroke for women who take either estrogen or estrogen plus progestin, as compared with those who do not take hormones, to be 0.96.[136] The analysis included observational studies that reported both increased and decreased risks of stroke in women who took estrogen. Data are limited concerning dose, duration of use, and the effects of the combined regimen of estrogen plus progestin. Also, data on subtypes of stroke are lacking. An analysis of data from the first National Health and Nutrition Examination Survey found an adjusted relative risk of stroke for women who had ever received hormone-replacement therapy, as compared with those who had never been treated, of 0.69 (95 percent confidence interval, 0.47 to 1.00), and a risk of fatal stroke of 0.37 (95 percent confidence interval, 0.14 to 0.92).[137]

Continued research is needed on estrogen-replacement therapy, particularly on the effects of the combination preparations that include progestins, which are currently used to avoid an increased risk of endometrial cancer. The Women's Health Initiative, a recently launched randomized clinical trial of hormone-replacement therapy, should provide conclusive evidence on postmenopausal hormone therapy and health outcomes, including stroke, in women.[138]

Healthy People 2000

The Healthy People 2000 program includes national health-promotion and disease-prevention objectives.[30] The objective concerning stroke is to reduce deaths from stroke to no more than 20 per 100,000 (the figure in 1991 was 26.8 per 100,000).[30] Table 2 presents the risk-reduction objectives for specific risk factors linked with stroke, along with an estimate of the base-line prevalence (from various periods before 1990) and the current prevalence of these risk factors, and suggested risk-reduction strategies.[139-141] A recent article gives a detailed evaluation of the progress to date toward achieving the objectives of Healthy People 2000.[142] As can be seen in Table 2, there have been decreases in the prevalence of hypertension, smoking, and high serum cholesterol levels since 1990, but the prevalence of physical inactivity and diabetes has remained the same. Obesity has increased during the period. Given this mixed record, we need to pay continued attention to the implementation of risk-reduction strategies and the development of programs that will fill in the gaps where current strategies are deficient.

Basic research is leading to an improved understanding of the pathogenesis of stroke, and a number of therapeutic strategies are now being tested in clinical trials. These approaches must overcome both the extreme susceptibility of brain cells to the effects of short periods of ischemia and the delays that typically occur before patients with stroke come to medical attention. The outcome of a patient with a treated stroke may never be as good as that of someone in whom a stroke is prevented. Until these research efforts come to fruition, prevention will be the key to alleviating the enormous human burden of stroke.

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